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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHANDRA, GYAN	
ART UNIT	**PAPER NUMBER**
1646	

DATE MAILED: 12/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/827,937	LI ET AL.	
	Examiner	Art Unit	
	Gyan Chandra	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-74* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 2/24/2004
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Group I, Claims 23-74, in the reply filed on 05/06/2003 is acknowledged. The traversal is on the ground(s) that though the Group I is an antibody and Group II is a method of using the antibody to screen a compound are representing two independent inventions, searching both the inventions would not be burdensome. This is not found persuasive because an application may properly be required to be restricted to two or more claimed inventions if they are able to support separate patents and they are either independent (MPEP § 806.04 - § 806.04 (i) or distinct (MPEP § 806.05 – § 806.05 (i)). The Examiner has shown that the Groups I and II are independent or distinct inventions for the reason in the previous office action (see Paper mailed on 02/06/2003). Furthermore, MPEP § 803 provides that the separate classification (i.e., class and subclass) of distinct inventions is sufficient to establish a prima facie case that the search and examination of the plural inventions would impose a serious burden upon the Examiner. For example, Group I is an antibody which specifically binds to the polypeptide of SEQ ID NO: 2, class 530, subclass 387.9, and Group II is drawn to a method of screening a compound, which is class 435, subclass 7.1. Further, searching for an antibody which specifically binds to a polypeptide of SEQ ID NO: 2, and searching for a method of identifying a compound would impose a serious search burden. Searches for an antibody which specifically binds to the polypeptide of SEQ ID NO: 2 and a method of screening a compound are not coextensive.

The requirement is still deemed proper and is therefore made FINAL.

The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Objection to the Specification

The objection to the specification for a new heading is withdrawn pursuant to Applicants' acceptance of the suggested title. The title "BRIEF DESCRIPTION OF THE FIGURES" has been made of record.

In view of Applicant's submission of "Statement Concerning the Deposited cDNA Clone" and the amendment to the specification to include the address of the ATCC, the objection to the specification has been withdrawn.

Claim Rejections - 35 USC § 112,Second Paragraph

The rejection of claims 39, 50, 65, and 74 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in response to Applicants' arguments.

Claim Rejections - 35 USC § 101 and 112, First Paragraph

The rejection of claims 23-74 are rejected under 35 U.S.C. 101 as not supported by either a specific and substantial asserted utility or a well established utility is

maintained. Applicants' arguments have been fully considered but they are not persuasive.

The claims are drawn to an isolated antibody/antibody fragment: (i) which specifically binds to the polypeptide of amino acids 1-342 or 2-342 of SEQ ID NO: 2, (ii) which specifically binds to the polypeptide encoded by the human cDNA in ATCC deposit NO.209003, and (iii) which specifically binds to the mature polypeptide produced upon cellular expression of the polypeptide encoded by the human cDNA in ATCC Deposit NO: 209003. Further, claims are drawn to a method of producing isolated antibody and antibody fragments.

The bases for these rejections is set forth at page 7-17 of the previous Office Action (mailed 06 February, 2003).

Applicant argues that the specification discloses the use of antibody as an antagonist to the polypeptide of amino acids 1-342 or 2-342 of SEQ ID NO: 2 and the specification discloses use of antagonists for teaching various diseases. The specification discloses that the polypeptide of amino acids 1-342 or 2-342 of SEQ ID NO: 2 has about 25% identity and 49% similarity to the EBI-1 gene over an approximately 350 amino acid stretch, page 7. EDG-2 (G protein coupled receptor of SEQ ID NO: 4) has about 54% identity and 73% similarity to the EDG-1 orphan G-protein coupled receptor, page 7. Both EBI-1 and EDG-1 are found in a variety of tissue and are themselves considered orphan receptors.

However, as was set forth in Brenner v. Manson, 383 U.S. 519 (1966), the instant invention lacks a specific and substantial real world utility absent elucidation of

the biological function of the disclosed protein agonist which the claimed antibody is directed and any role that the antibodies identified as modulators of the protein would play in modulation or identification of any disease state associated with that biological function. Without further research and experimentation, the claimed antibodies do not provide an immediate benefit to the public. The biological research contemplated using applicants' antibodies is to take place sometime in the future, only after elucidation of the biological role of the polypeptide of amino acid sequence of SEQ ID NO: 2. However, no disclosure is provided within the instant specification as to any specific biological function of the polypeptide having SEQ ID NO: 2 or any specific disease where the claimed invention could be used. Speculating a function of a protein merely based on homology is not predictive. Any benefit to the public is speculative, at best.

Applicant argues that there is at least one specific utility for the claimed antibody. Applicants' argument has been fully considered but is not found to be persuasive. Applicant argues that the claimed antibody can be used for the detection of heart disease among the diseases. However, the claimed antibody is directed against the protein of SEQ ID NO: 2, which is an orphan receptor without a known ligand and whose biological function is unknown. The specification does not disclose a nexus between the orphan receptor and heart disease or any other pathological condition for that matter. The fact that the protein is an orphan receptor indicates that its role in any putative disease progress has yet to be elucidated. In the absence of any data as to the receptor's biological function, there is no basis upon which to base a specific or substantial utility for the claimed antibody.

Applicant argues that the claimed invention has at least one asserted, specific utility which is substantial. This has been fully considered but is not found to be persuasive. Applicants assert that the specification [0035, page 8, 0097, page 23, 0098, page 24, 0099, page 24], discloses a role of the claimed invention in potential diverse therapeutic and diagnostic applications including mental disorders, cancer, migraine, eating disorders, asthma, heart disease, psychoses, restenosis, Alzheimer's disease, Parkinson's disease, atherosclerosis and a number of others. The applicants' disclosure provides a large list of diseases allegedly associated with the polypeptide of SEQ ID NO: 2, but fails to disclose the specific role of the disclosed protein in any of these diseases. Further, Applicants point to a publication by Wang et al., in Arteriosclerosis. Thromb. Vasc. Biol. (year 2003) that they have disclosed that an EBI-2 receptor antagonist blocked ADP-induced platelet aggregation in a canine coronary thrombosis model and suggests a role for such an agent in treating myocardial infarction. Applicant points to the findings of Hollopeter et al. (2001) that they have linked P_2Y_{12}, which applicant claims is the same as EBI-2, in ADP mediated platelet aggregation. Hollopeter et al. teach that ADP mediated platelet aggregation is rendered through two different receptors (i) P_2Y_1 and P_2Y_{12} and platelets play crucial role in the maintenance of homeostasis, any perturbation in the homeostasis could lead to pathological thrombus formation and vascular occlusion resulting in stroke, myocardial infarction and unstable angina. Applicant further adds that Chattaraj (2001) uses the antagonist molecule for treating angina. However, these are not persuasive because the specification does not disclose any specific association of the protein of SEQ ID NO: 2 with any of these

disease conditions. Therefore, an antibody which specifically binds to the protein of SEQ ID NO: 2, for which the function is unknown does not have specific and substantial real world utility. Applicants point to the findings of Wang, Hollopeter and Chattaraj in order to establish a utility of the instant invention. However, Applicants have failed to disclose an asserted, substantial and specific utility of their invention in the specification at the time filing the instant application.

In re Kirk, 153 USPQ 48, 53 (CCPA 1967) quoting the Board of Patent Appeals, " We do not believe that it was the invention of the status to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates."

Claim Rejections - 35 USC § 112, First Paragraph

The rejection of claims 23-74 under 35 USC § 112, first paragraph, as lacking enablement, is maintained.

Claims 23-74 also remain rejected under 35 U.S.C. 112, first paragraph. Since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the

reason set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Applicants' disclosure provides guidance as to how to make an antibody for the protein of SEQ ID NO: 2; however, it does not disclose a specific biological function of the protein of SEQ ID NO: 2 or any method of using antibodies directed against the protein. Applicants' disclosure fails to provide sufficient guidance to enable one of skill in the art to be able to use the claimed specific antibody or the protein for any diagnostic or therapeutic purpose without undue experimentation.

The rejection of claims 39, 50, 65 and 74 under 35 U.S.C. 112, first paragraph – enablement for the method of producing the antibody has been withdrawn. Applicants' arguments, (submitted with the amendment of 06 May 2003) have been fully considered and are persuasive.

Claim Rejections - 35 USC § 112, First Paragraph – Written Description

The rejection of claims 39, 65, 50 and 74 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn. Applicants' amendment and arguments are persuasive.

Claim Rejections - 35 USC § 112, First Paragraph- Deposit Rules

The rejection of claims 51-74 under 35 U.S.C. 112, first paragraph, for the deposit of the cDNA clone is withdrawn persuasive to applicants' statement filed on 4/30/03.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

Claims 29 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being vague and indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is not clear how " hybridoma technique" differ from the human B-cell hybridoma technique and the EBV-hybridoma technique. Further, it is unclear which hybridoma technique claim 30 refers back to.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 36 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim is drawn to an isolated antibody which specifically binds to the polypeptide of amino acids 1-342 of SEQ ID NO: 2 and the claimed antibody is produced in transgenic

mice. The claim requires producing a transgenic mouse using that will express an antibody which specifically binds to the polypeptide of SEQ ID NO: 2.

In analyzing whether the written description requirement is met, first it is determined whether a complete structure of the transgenic mouse has been described. Since it is not realistic to expect that the "complete structure" of any transgenic mouse, or even a cell, could be described, this requirement is interpreted to be whether phenotypic consequences or other characteristics of the mouse resulting from altering the genotype have been described. In the instant case, the claimed invention encompasses a transgenic mouse which produces an antibodies.

In the case of a transgenic mouse, its complete structure will be the description of its genome and the gene/polynucleotide that has been introduced into the genome and is expressed in the transgenic mouse. The specification fails to teach complete structure of the transgenic mouse because it does not teach what transgene is comprised in the genome.

Next, it is determined whether the specification described the claimed invention by its other identifying characteristics. In the case of transgenic mouse such other characteristics would be the phenotypic consequences of expressing the transgene.

The specification as filed does not teach which gene/polynucleotide was used to make the transgenic mouse. The specification also fails to disclose what was the result of introducing the gene/polynucleotide into the genome of the transgenic mouse. At the time of invention, it was unpredictable whether one could produce a transgenic mouse from any gene and it was unpredictable what would be the characteristics of the

transgenic mouse. For example, Wood stated (Comp. Med. 50: 12-15, 2000) stated that the phenotype of a mouse is determined by a complex interaction of genetics and environment. It is the evaluation of the phenotype that allows us to determine the usefulness of a transgenic strain as a model for biomedical research including production of antibodies. A specific phenotype is usually expected from genetically altered mice where a particular gene function has been modified or ablated altogether. Thus for any given genetic alteration, we often try to predict what the phenotype will be. Often we find the predicted phenotype, surprisingly, produced "no phenotype".

This clearly indicates that the phenotype of a transgenic mouse comprising any gene in its genome could not be predicted at the time of invention. The specification fails to describe any characteristic of a transgenic mouse that could be used for producing the claimed antibody.

This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, & 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Vas-Cath Inc. V. Mahurka, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is *whatever is now claimed* (see page 1117). The specification does

not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (see *Vas-Cath* at page 1116).

As discussed above, the skilled artisan could not envision the detailed phenotype and structure of the transgenic mouse until reduction to practice has occurred, regardless of the complexity or simplicity of the method of making and isolating it. With the limited information disclosed in the specification, an artisan would have not been able to predict whether a mouse would have structure to produce the claimed antibody. Therefore, the limited disclosure in the specification is not sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the mouse recited in the claims at the time of the application was filed. Thus the specification fails to provide the written description of the claimed invention to the breadth of the claims.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Claim 36 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the

same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977) and have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

The Nature of the Invention: The claimed invention is drawn to an antibody which specifically binds to the polypeptide of SEQ ID NO: 2, and the claimed antibody is produced in transgenic mice. Producing the antibody as claimed in instant application will require making a transgenic mouse that expresses the claimed antibody.

The state of the prior art and the predictability or lack thereof in the art:

While the method of making a transgenic mouse has become more routine using general protocols, the selection of a particular promoter, expression of a transgene to a particular tissue or in all the tissues, expression of the transgene during a certain stage of development or after maturity, method of introduction of the transgene in the oocyte or using embryonic stem cells for producing the transgenic mouse are some of the factors that make even making of transgenic mouse unpredictable. In an assessment of the transgenic technology at the time of the invention, Cameron (Molecular Biotechnolgy 7:253-265, 1997) noted, " Well regulated transgene expression is the key to successful transgenic work, but all too often experiments are blighted by poor levels or the complete absence of expression, as well as less common problems, such as leaky expression in nontargeted tissues. A feature common to many transgenic experiments is the unpredictable transgenic lines produced with the same construct frequently displaying different levels of expression. Further, expression levels do not correlate with the number of transgene copies integrated. Such copy-number-independent expression patterns emphasize the influence of surrounding chromatin on the transgene" (see page 256, section 4 on transgene regulation and expression). Additionally, function of promoters and enhancer elements may require specific cellular factors and therefore may not be functional in a mouse or any other animal species. The specification does not provide any guidance as to what promoter was used for expressing an exogenous gene such that the gene would have been expressed in the transgenic mouse so that the claimed antibody could be produced in sufficient amounts.

If not, what steps would have been taken to address this? Additionally, the specification fails to teach the transgene that would have encoded the claimed antibody, what was the vector used or what was the structure of the construct used for making the transgenic mouse.

The amount of direction and guidance present and the presence or absence of working examples: Given the teachings of unpredictability found in the art, detailed teachings are required to be present in the disclosure in order to enable the skilled artisan to practice the invention as claimed. These teachings are absent. The disclosure points to the US patent NO. 4,946,778 for the production of single chain antibodies, however the patent does not teach how to construct and produce the transgenic mice of the claimed invention for producing the claimed antibody.

The breadth of the claims and the quantity of experimentation needed: Because the claims encompass producing antibody which binds to polypeptide of SEQ ID NO: 2 and the claimed antibody is produced in the transgenic mice, in the light of the teachings of the unpredictability found in the art discussed and because of the supra lack of sufficient teachings in applicants disclosure to overcome those teachings, it would require undue experimentation by one of skill in the art to be able to practice the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gyan Chandra whose telephone number is (571) 272-2922. The examiner can normally be reached on 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gyan Chandra
AU 1646
14 December 2004

JANET ANDRES
PRIMARY EXAMINER